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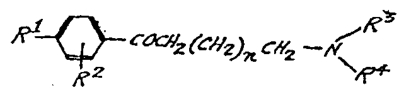
(54) AMINOALCOHOLS AND THEIR CONVERSION TO AMINOKETONES

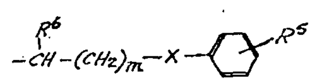
(71) We, SUMITOMO CHEMICAL COMPANY LIMITED, a corporation organised under the laws of Japan, of 15, Kitahomo-5-chome, Higashi-ku, Osaka, Japan, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to a process for producing therapeutically active aminoketones and to intermediates for the production thereof.

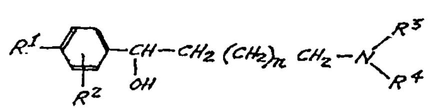
More particularly, the present invention relates to a process for producing an aminoketone of the formula,



wherein R^1 is a hydrogen or halogen atom, or a C_1—C_4 alkyl, C_1—C_3 alkoxy or trifluoromethyl group; R^2 is a hydrogen or halogen atom, or a C_1—C_3 alkoxy or amino group; R^3 is a hydrogen atom, or an alkyl, phenyl or benzyl group; R^4 is an alkyl, cycloalkyl, or phenyl group, which phenyl group may optionally be substituted by a halogen atom, or a group having the formula,



(in which R^5 is a hydrogen or halogen atom, or a C_1—C_4 alkyl, C_1—C_3 alkoxy, or trifluoromethyl group; R^6 is a hydrogen atom, or a phenyl or C_1—C_3 alkyl group; X is an oxygen or sulfur atom or represents a single bond; and m is 0, 1, 2 or 3); and n is 0, 1, 2, 3 or 4, or an acid addition salt thereof, and relates to novel aminoalcohols of the formula,



wherein R^1, R^2, R^3, R^4 and n are as defined above, or acid addition salts thereof.

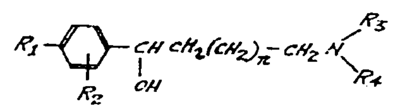
In the above definitions, preferred groups of R^1 are for example, fluorine, chlorine, methoxy, ethoxy, isopropoxy, methyl, ethyl, isopropyl, tertiary butyl, and trifluoromethyl; preferred groups of R^2 are, for example, hydrogen, fluorine, chlorine, amino and methoxy; preferred groups of R^3 are, for example, hydrogen, methyl, ethyl, n-propyl, n-butyl, phenyl, and benzyl; preferred groups of R^4 are for example, methyl,

ethyl, n-propyl, n-butyl, cyclopropyl, cyclopentyl, cyclohexyl, phenyl, ω-phenylalkyl, ω-phenoxyalkyl, and ω-phenylthioalkyl in which the ω-phenyl group may be further substituted by a methyl, ethyl, isopropyl, tertiary butyl, methoxy, ethoxy, isopropoxy, fluorine, chlorine, bromine, or trifluoromethyl group.

As is known, the above specified aminoketones can be used as tranquillizers, spasmolytic agents or adrenolytics and methods for the production of such compounds have been proposed in the literature (U.S. Patent 3,189,600 and Belgian Patent 668,124). Previously reported processes have not been found to be satisfactory for a large scale commercial operation.

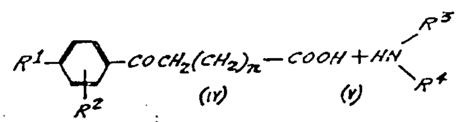
The present invention, however, provides a process which can afford a novel improved and advantageous method of manufacturing the above-mentioned aminoketones. It, also, provides a range of compounds which can be used as intermediates in the preparation of the aminoketones.

According to the method aspect of the present invention an aminoketone of the formula given and defined above is prepared by reacting an aminoalcohol of the formula,

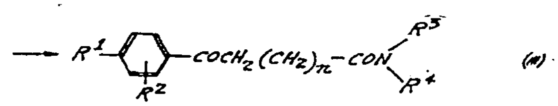


wherein R_1, R_2, R_3, R_4 and n are as defined above, with an oxidizing agent, and optionally salinating the resultant product.

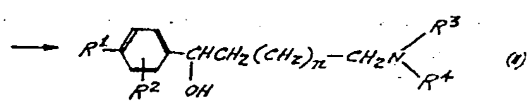
Using processes within the present invention, the desired aminoketone compounds can be produced by the steps illustrated and defined in the following reaction scheme:



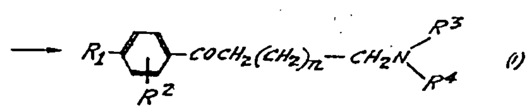
First step



Second step



Third step



In the formulae, R^1, R^2, R^3, R^4 and n are as defined above.

The condensation reaction, i.e. the first step of the process, can be conducted as follows:

A ω-benzoylalkanoic acid of the formula (IV), or its active derivative, is reacted with an amine of the formula (V) in a suitable solvent.

The said active derivative of the ω-benzoylalkanoic acid can for example, be the chloride, bromide, anhydride, a mixed anhydride or the p-nitrophenyl ester. The mixed anhydrides mentioned above include those prepared from ethyl chloroformate, or isobutyl chloroformate.

The reaction solvent preferably employed is a solvent which is inert under the conditions of the reaction and selected from ether, tetrahydrofuran, toluene, chloroform, acetone, ethyl acetate, or dimethyl formamide.

The reaction is preferably carried out in the presence of a basic agent or condensing agent such as pyridine, triethylamine, sodium carbonate, sodium hydroxide, or dicyclohexylcarbodiimide. In general, the reaction is carried out at a temperature within a range of from about $-20°C$ to about $80°C$, and the yield of the amidoketone is about 85% or more.

The reduction reaction, i.e. the second step of the process, can be conducted as follows:

An amidoketone of the formula (III) is reacted with a suitable reducing agent in a solvent which is inert under the conditions of the reaction. Suitable reducing agents include hydrides such as lithium aluminium hydride, diborane, or a mixture of sodium borohydride and aluminium chloride, and a mixture of sodium borohydride and boron trifluoride. The preferred reaction solvents include diethyl ether, diisopropyl ether, tetrahydrofuran, dioxane, methylal, N-ethyl-morpholine, ethylene glycol dimethyl ether, diethylene glycol dimethyl ether, and toluene.

The reaction is preferably carried out at a temperature within a range of from about 0°C to 100°C, using a stoichiometric amount, or an excess of the said reducing agent.

It is particularly preferred to use lithium aluminum hydride in refluxing ether, tetrahydrofuran, toluene or a mixture of these solvents.

After the reaction is complete, the product can be isolated by conventional methods well known in the art in a yield above 90%. The aminoalcohol (II) thus obtained may be converted into an acid addition salt thereof using conventional methods. Such salts include those prepared from both organic and inorganic acids, such as, for example, hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric, acetic, fumaric, benzoic, tartaric, oxalic, citric, succinic, glycolic, salicylic, cinnamic, mandelic and ascorbic aids.

The oxidation reation i.e. the third step of the process, can be conducted as follows:

The aminoalcohol of the formula (II) or an acid addition salt thereof is reacted with an appropriate oxidizing agent in a suitable organic or aqueous solvent.

The preferred oxidizing agents include chromium trioxide, chromic acid, dimethyl sulfoxide and manganese dioxide, although others such as permanganates, dichromates, oxygen, ozone, and peracids may be used. These oxidizing agents are preferably used in a stoichiometric amount or in excess. The reaction solvent, or the medium or diluent used somewhat depends on the oxidizing agent employed, but, in general, is selected from water, sulfuric acid, formic acid, acetic acid, acetone, chloroform, pyridine, toluene, dimethyl sulfoxide, and dimethyl formamide. The reaction is favourably carried out at room temperature or below, but higher temperatures are sometimes employed to accelerate the reaction.

In general, the reaction is essentially completed in a reaction time of from several minutes to several hours and the product of the reaction can be isolated from the reaction mixture by conventional methods in a yield of about 90% or more.

In general the products thus obtained are substantially pure and are optionally further purified by recrystallization.

Acid addition salts thereof are also optionally prepared by methods well known in the art. A variety of organic or inorganic acids are used for the purpose and examples thereof include those mentioned in the above description of the second step of the process. In addition to the above description, a further characteristic of the invention will be demonstrated by referring to the pharmacological properties of the intermediate amino alcohols within the present invention.

Pharmacological measurements using standard animal test procedures have demonstrated that the aminoalcohols within the present invention hereinafter called "the present compounds", possess a beneficial biological activity. More particularly, the present compounds have excellent central nervous or peripheral nervous system depressive activities. Thus, they are quite useful not only as intermediates used in the present process but also as therapeutic agents.

Each of these compounds may be brought into a form suitable for administration by a known method. For the preparation of a pharmaceutical composition, they may be mixed with carriers, diluents, lubricants, fillers and/or binders such as lactose, sucrose, calcium phosphate, starch, talcum, casein, magnesium stearate, methyl cellulose, polyglycols, and tragacanth, sometimes together with stabilizers and emulsifying agents. The resulting mixture may be processed in a conventional manner to form, for example, tablets, capsules, pills, or ampoules. The usual oral dosage of the active ingredient is between about 1 mg and about 400 mg daily.

As described above, it may safely be said that the process generally described

above can be used to provide an excellent manufacturing method, which is simple to operate, gives high yields, high purity of the products, utilizes easily available starting materials, IV and V, and provides valuable intermediates in the course of the process.

The present invention is further illustrated in more detail with reference to the following specific Examples.

Example 1

(Step 1)

To a stirred solution of 10 g of 3-benzoyl-propionic acid and 5.7 g of triethylamine in 120 ml of tetrahydrofuran was added dropwise 6.1 g of ethyl chloroformate at a temperature below 0°C. After the addition was completed, to the mixture was added 7.2 g of p-chloroaniline and the resulting mixture was stirred at room temperature for 4 hours. The reaction mixture was filtered and the filtrate was concentrated to dryness under reduced pressure.

Recrystallization of the residue from aqueous ethanol gave N-(p-chlorophenyl)-3-benzoylpropionamide melting at 168°—169°C.

(Step 2)

To a mixture of 4.2 g of lithium aluminum hydride and 60 ml of tetrahydrofuran was added dropwise a solution of 9 g of N-(p-chlorophenyl)-3-benzoylpropionamide in 80 ml of tetrahydrofuran. The resulting mixture was heated under reflux for 2 hours and allowed to cool. To the cooled mixture was added dropwise a solution of 30 ml of water and 70 ml of tetrahydrofuran. The solid which was separated was filtered off and the filtrate was concentrated to give N-(p-chlorophenyl)-1-phenyl-4-amino-1-butanol, which was treated with ethanolic oxalic acid to yield the oxalate melting at 90°—92°C.

(Step 3)

To a stirring solution of 4 g of N-(p-chlorophenyl)-1-phenyl-4-amino-1-butanol in 60 ml of chloroform was added 8 g of finely powdered manganese dioxide in portions at a temperature below 0°C. Stirring was continued for 6 hours at a temperature below 10°C and filtered. The filtrate was concentrated to a residue, which was recrystallized from ethyl acetate—hexane to give N-(p-chlorophenyl)-4-aminobutyrophenone melting at 116°—117°C. Using a method similar to that of steps 1 and 2 in example 1, the following compounds under (1) and (2) respectively were obtained.

(1)

N-Benzyl-3-(p-fluorobenzoyl)-propionamide, m.p.: 125°—126°C
N-Phenyl-3-(p-fluorobenzoyl)-propionamide, m.p.: 133°—135°C
N-Cyclohexyl-3-(p-fluorobenzoyl)-propionamide, m.p.: 138°—139°C
N-(1,2-Diphenylethyl)-3-p-fluorobenzoyl)-propionamide, m.p.: 106°—107°C
N-(2-Phenylethyl)-3-(p-fluorobenzoyl)-propionamide, m.p.: 104°—105°C
N-(1-Phenylethyl)-3-(p-fluorobenzoyl)-propionamide, m.p.: 130°—131°C
N-Benzyl-1-(p-fluorophenyl)-4-amino-1-butanol, m.p.: 78°—79°C
N-Phenyl-1-(p-fluorophenyl)-4-amino-1-butanol hydrochloride, m.p.: 131°—133°C
N-Cyclohexyl-1-(p-fluorophenyl)-4-amino-1-butanol, m.p.: 72°—73°C
N-(1,2-Diphenylethyl)-1-(p-fluorophenyl)-4-amino-1-butanol hydrochloride, m.p.: 197°—198°C
N-(2-Phenylethyl)-1-(p-fluorophenyl)-4-amino-1-butanol hydrochloride, m.p.: 114°—116°C
N-(1-Phenylethyl)-1-(p-fluorophenyl)-4-amino-1-butanol hydrochloride, m.p.: 126°—128°C

Example 2

To a stirred solution of 10.4 g of 3(p-fluorobenzoyl)propionic acid and 6.0 g of triethylamine in 120 ml of tetrahydrofuran was added dropwise 6.0 g of ethyl chloroformate at a temperature below −5°C. Stirring was continued for half an hour, and a solution of 9.6 g of 2-(o-ethoxyphenoxy)ethylamine in 10 ml of tetrahydrofuran was then added to the mixture. Further stirring was continued at room temperature for 4 hours. The reaction mixture was filtered and the filtrate was concentrated to a residue under reduced pressure. 11 Grams of residual N-[2-(o-ethoxyphenoxy)-ethyl]-3-(p-fluorobenzoyl)propionamide was added in several portions to a stirring mixture of 3.6 g of lithium aluminum hydride and 130 ml of tetrahydrofuran. The resulting mixture was heated to 65°C and refluxed for 3 hours. To the

cooled reaction mixture was added dropwise a solution of 20 ml of water and 60 ml of tetrahydrofuran.

After standing for 30 minutes, the whole was filtered, washed with 60 ml of tetrahydrofuran and the combined filtrate and washings were concentrated under reduced pressure.

The residue was extracted with 200 ml of ether. Concentration of the extract gave N - [2 - (o - ethoxyphenoxy)ethyl] - 1 - (p - fluorophenyl) - 4 - amino - 1-butanol.

To a solution of 5.5 g of the above product and 11 ml of water in 100 ml of acetone was added a solution of 2 g of chromium trioxide in 14 ml of water and 3 g of concentrated sulfuric acid under stirring at 5°C.

After the addition was completed, the resulting mixture was allowed to warm and further stirring was continued for one hour at room temperature. The reaction mixture was made alkaline by addition of a 15% aqueous solution of sodium hydroxide and was diluted with 55 ml of methyl isobutyl ketone.

The organic layer separated was concentrated under reduced pressure to a residue. The residue was washed with water and then agitated with 30 ml of cold 6 N hydrochloric acid and the resulting insoluble matter was collected by filtration to give N - [2 - (o - ethoxyphenoxy)ethyl] - 4 - amino - p - fluorobutyrophenone hydrochloride melting at 110°—112°C after recrystallization from aqueous acetone.

By a procedure similar to that of example 2, the following compounds were obtained:

N-[2-(o-Ethoxyphenoxy)ethyl]-N-methyl-4-amino-p-fluorobutyrophenone hydrochloride, m.p.: 113°C

N-[2-(o-Ethoxyphenoxy)ethyl]-N-ethyl-4-amino-p-fluorobutyrophenone hydrochloride, m.p.: 144°C

N-[2-(o-Ethoxyphenoxy)ethyl]-4-amino-p-chlorobutyrophenone hydrochloride, m.p.: 127°—128°C

Example 3

To a stirred solution of 0.03 mole of 5-(m,p-dimethoxybenzoyl)valeric acid and 0.033 mole of triethylamine in 200 ml of toluene was added dropwise 0.03 mole of ethyl chloroformate while the temperature was kept below —5°C. Stirring was continued at 0°C for half an hour, the mixture was added and 0.03 mole of N-[1-methyl-2-(p-methoxyphenyl)]-ethylamine was then added to the mixture in portions. The resultant mixture was allowed to stand overnight. The reaction mixture was washed successively with water, diluted hydrochloric acid, diluted aqueous sodium hydroxide and finally water. The resulting solution was concentrated to dryness giving N-ethyl-N-[1-methyl-2-(p-methoxyphenyl)ethyl]-5-(3,4-dimethoxybenzoyl)-valeramide.

The product thus obtained was reduced with lithium aluminum hydride in tetrahydrofuran by the procedure as described above in step 2 of example 1 to give N-ethyl - N - [1 - methyl - 2 - (p - methoxyphenyl)ethyl] - 1 - (m,p - dimethoxyphenyl) - 6 - amino - 1 - hexanol.

To a solution of 6.6 g of N-ethyl-N-[1-methyl-2-(p-methoxyphenyl)ethyl]-1-(3,4-dimethoxyphenyl)-6-amino-1-hexanol and 13 ml of water in 120 ml of acetone was added a solution of 2 g of chromium trioxide in 14 ml of water and 3 g of concentrated sulfuric acid while stirring at a temperature below 10°C. The reaction mixture was stirred at 25°C for one hour, cooled, made alkaline with 15% sodium hydroxide and diluted with 90 ml of hot acetone. The organic layer was isolated, diluted with 90 ml of water, concentrated to a volume of about 100 ml and extracted with 100 ml of benzene. The extract was washed with water, dried over anhydrous sodium sulfate and thereto was added 16 ml of 10% methanolic hydrogen chloride. The resulting solution was concentrated to dryness under reduced pressure.

Recrystallization of the residue from isopropyl alcohol-ether gave N- - ethyl-N - [1 - methyl - 2 - (p - methoxyphenyl)ethyl] - 6 - amino - m,p - dimethoxyhexanophenone hydrochloride melting at 108°—111°C.

By a procedure similar to that of Example 3, the following compounds were obtained:

N,N-Dimethyl-4-amino-p-chlorobutyrophenone hydrochloride, m.p.: 170°—172°C

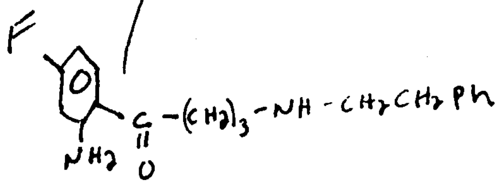
N,N-Diethyl-4-amino-p-chlorobutyrophenone hydrochloride, m.p.: 124°—127°C

N,N-Diethyl-4-amino-p-isopropylbutyrophenone hydrochloride, m.p.: 90°C

N-Benzyl-N-methyl-4-amino-p-fluorobutyrophenone hydrochloride, m.p.: 153°—155°C

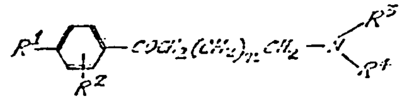
N-Methyl-N-(1-methyl-2-phenylethyl)-4-amino-p-fluorobutyrophenone hydrochloride, m.p.: 135°—136°C

N'-(2-Phenylethyl)-4-amino-o-amino-p-fluorobutyrophenone hydrochloride, m.p.: 196°—200°C



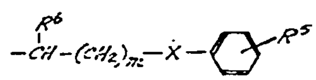
WHAT WE CLAIM IS:—

1. A process for producing an aminoketone of the formula,

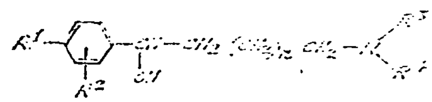


(I)

wherein R^1 is a hydrogen or halogen atom, or a C_1—C_4 alkyl, C_1—C_3 alkoxy or trifluoromethyl group; R^2 is a hydrogen or halogen atom, or a C_1—C_3 alkoxy or amino group; R^3 is a hydrogen atom, or an alkyl, phenyl or benzyl group; R^4 is an alkyl, cycloalkyl, or phenyl group, which phenyl group may optionally be substituted by a halogen atom, or a group having the formula,



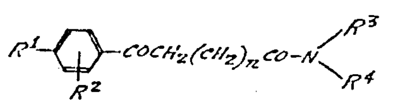
(in which R^5 is a hydrogen or halogen atom, or a C_1—C_4 alkyl, C_1—C_3 alkoxy or a trifluoromethyl group; R^6 is a hydrogen atom, or a phenyl or C_1—C_4 alkyl group; X is an oxygen or sulfur atom or represents a single bond; and m is 0, 1, 2 or 3); and n is 0, 1, 2, 3 or 4, or an acid addition salt thereof, which includes reacting an aminoalcohol of the formula,



(II)

wherein R^1, R^2, R^3, R^4 and n are as defined above, or an acid addition salt thereof, with an oxidizing agent and optionally salinating the resultant product.

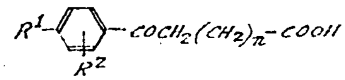
2. A process according to claim 1 which includes the preliminary step of preparing the aminoalcohol of the formula (II), or an acid addition salt thereof, by reacting an amidoketone of the formula,



(III)

wherein R^1, R^2, R^3, R^4 and n are as defined in claim 1, with a reducing agent.

3. A process according to claim 2 which includes the preliminary step of preparing the amidoketone of the formula (III) by reacting an ω-benzoylalkanoic acid of the formula,



wherein R^1 and R^2 are as defined in claim 1, or an active derivative thereof, with an amine of the formula,

$$HN\begin{matrix} \diagup R^3 \\ \diagdown R^4 \end{matrix}$$

wherein R^3 and R^4 are as defined in claim 1.

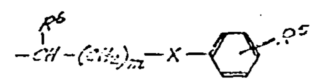
4. A process according to claim 1 wherein the said oxidizing agent is chromium trioxide, chromic acid, manganese dioxide or dimethyl sulfoxide.

5. A process according to claim 2 wherein the said reducing agent is a hydride.

6. A process according to claim 5 wherein the hydride is lithium aluminium hydride.

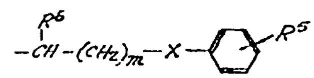
7. A process according to claim 3 wherein the active derivative of the ω-benzoylalkanoic acid is a mixed anhydride prepared from alkyl haloformates.

8. A process according to any one of the preceding claims, wherein R^1 is fluorine; R^2 is hydrogen; and R^4 is a group of the formula.



in which R^5, R^6, X and m are as defined in claim 1.

9. A process according to any one of claims 1 to 7, wherein R^1 and R^2 are each a methoxy group at the same time; and R^4 is a group of the formula



in which R^5, R^6, X and m are as defined in claim 1.

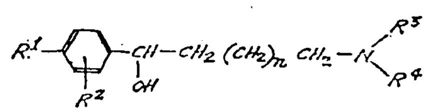
10. A process according to claim 8 wherein N-[2-(o-ethoxyphenoxy)ethyl]-1-(p-fluorophenyl)-3-amino-1-butanol is reacted with chromic acid to yield N-[2-(o-ethoxyphenoxy)ethyl]-4-amino-p-fluorobutyrophenone.

11. A process according to claim 9 wherein N-ethyl-N-[1-methyl-2-(p-methoxyphenyl)ethyl]-1-(m,p-dimethoxyphenyl)-6-amino-1-hexanol is reacted with chromic acid to yield N-ethyl-N-[1-methyl-2-(p-methoxyphenyl)ethyl]-6-amino-m,p-dimethoxyhexanophenone.

12. A process according to claim 10 which includes the preliminary step of reacting N-[2-(o-ethoxyphenoxy)ethyl]-3-(p-fluorobenzoyl)propionamide with lithium aluminum hydride to yield the N-[2-(o-ethoxyphenoxy)ethyl]-1-(p-fluorophenyl)-4-amino-1-butanol.

13. A process according to claim 11 which includes the preliminary step of reacting N - ethyl - N - [1 - methyl - 2 - (p - methoxyphenyl)ethyl] - 5 - (m,p - dimethoxybenzoyl)valeramide is reacted with lithium aluminum hydride to yield the N-ethyl - N - [1 - methyl - 2 - (p - methoxyphenyl)ethyl] - 1 - (m,p - dimethoxyphenyl) - 6 - amino - 1 - hexanol.

14. A compound of the formula,



wherein R^1, R^2, R^3, R^4 and n are as defined in claim 1, or an acid addition salt thereof.

15. A pharmaceutical composition containing one or more compounds as claimed in claim 14 and a pharmaceutically acceptable diluent or carrier.

16. Processes for producing aminoketones of the formula (I), given and defined in claim 1 substantially as herein described and exemplified.

17. Aminoketones of the formula (I), given and defined in claim 1 whenever prepared by a process according to any one of claims 1 to 13 and 16.

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